LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Annual pharmacovigilance report 2016 of the Danish Medicines Agency

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Contents

1 Introduction

When a new medicine is authorised and marketed, it has been tested in a defined and well-controlled patient group. We therefore know the medicine's effect and the most frequent adverse reactions. To ensure safety for medicine users, it is vital that we know the medicine's profile of adverse drug reactions after it has been taken into use.

Important knowledge and relevant data about possible adverse reactions and safety problems of medicines are found in several places, including in the health service, the industry, the research environment and among medicine users. The Danish Medicines Agency, DKMA, expects to see increasing numbers of data sources that can give us more knowledge about new potential safety issues in the coming years, and we will pay attention to this development.

Many sources of knowledge about possible safety issues

The reporting of suspected adverse reactions is a crucial source of knowledge about possible medicine safety issues after market entry and thus a key element in pharmacovigilance (the monitoring of the safety of medicines). The DKMA uses a pharmacovigilance system to monitor medicines safety and keeps a register of reported suspected adverse reactions.

Physicians are an important source of knowledge when it comes to ensuring pharmaceutical safety for medicine users when they report suspected adverse reactions to the DKMA[1]. They are the ones closest to the medicine users, and they know the course of the disease and can observe how the medicine is tolerated in their patients. The more adverse reactions physicians report, the better our basis becomes to change the recommendations for treatment with a certain product or make other improvements.

Correspondingly, the information we receive from medicine users when they report adverse reactions to the DKMA is very important.

We may also learn about a safety issue from safety updates – i.e. new knowledge about adverse reactions that pharmaceutical companies must currently prepare and submit to the DKMA for assessment. Other important sources of pharmaceutical safety issues include ADR signals[2] from other countries or from other national authorities, organisations, institutions, like the Danish Patient Safety Authority, patient organisations, physicians and pharmacists.

Sometimes the media may also be a route to knowledge about a new medicine safety problem, which the DKMA may decide to investigate further.

To secure a strong basis for the work with pharmacovigilance, we collaborate with other European medicines agencies by exchanging information about new potential signals, and there is good opportunity to discuss the issues at the monthly meetings in the European Pharmacovigilance Risk Assessment Committee, PRAC, which the DKMA attends.

[1] Physicians in Denmark are bound by law to report certain types of adverse reactions if they suspect that an adverse reaction is caused by one or several medicines. This appears from executive orders no. 1823 of 15 December 2015 on reporting of adverse reactions of medicinal products, etc. and no. 898 of 23 June 2016 on monitoring of adverse reactions from medicinal products.

[2] An ADR signal reflects a new possible causal relationship between an adverse reaction and a certain type of medicine or a new angle on an already known causality.

This annual report provides insights into the DKMA's work with pharmacovigilance – with a special focus on reporting figures for 2016 and the ADR signals the DKMA has worked with.

2 Summary

The number of reports on suspected adverse reactions submitted to the DKMA in 2016 more or less levelled the year before. We received less ADR reports from physicians, but ADR reports involving patient compensation cases from the Patient Compensation Association accounted for a larger share than previous years.

Recent years have shown a clear trend that regions with an ADR manager role report more adverse reactions than the regions with no ADR manager role. But this trend has not been as marked in 2016, which recorded a fall in ADR reports especially from the Capital Region of Denmark compared to 2015. In the coming time, our focus will therefore be to strengthen ADR reporting in the regions.

Our focus areas in 2016 included contraceptive pills, melatonin use in children and adolescents, HPV vaccines and biological medicines and biosimilars, which we monitor routinely. We were also very active on the international scene and participated in several European collaborations.

A five-year strategy with a clear vision and mission for the work of the Danish Medicines Agency prompted a new internal organisation in 2016 as well as new area-specific strategies – including a new pharmacovigilance strategy. In the coming years, we aim to strengthen our international position, develop improved ADR signal detection and will increasingly involve medicine users more in our work to ensure optimum safety for users.

3 ADR reports in 2016

Reports on suspected adverse reactions contribute with important knowledge about medicines safety and are a crucial element in our combined pharmacovigilance activities, which ultimately secure the best treatment for medicine users.

At the DKMA, we continually strive to improve the possibilities of reporting suspected adverse reactions, ensure qualitative ADR reports and raise awareness of the usefulness and importance of reporting.

The number of ADR reports levels 2015
After some years of rising numbers of reported suspected adverse reactions, there were no major differences in figures in 2016 compared to 2015.

Number of ADR reports in 2016	
Number of ADR reports (including duplicates)[3]	7,654
Number of ADR reports (excluding duplicates)	7,160
Serious ADR reports[4]	2,856 (37%)
Non-serious ADR reports	4,798 (63%)

TABLE 1. TOTAL NUMBER OF REPORTS OF SUSPECTED ADVERSE REACTIONS IN 2016 AND THE SHARE OF SERIOUS AND NON-SERIOUS ADR REPORTS.

In 2016, we received altogether 7654 ADR reports, which is more or less the same as the 7538 ADR reports received in 2015.

37% of the total number of ADR reports were classified as serious. The ratio of serious ADR reports to non-serious ADR reports was about the same as the previous two years, but the number of serious ADR reports fell slightly in 2016 (figure 1).

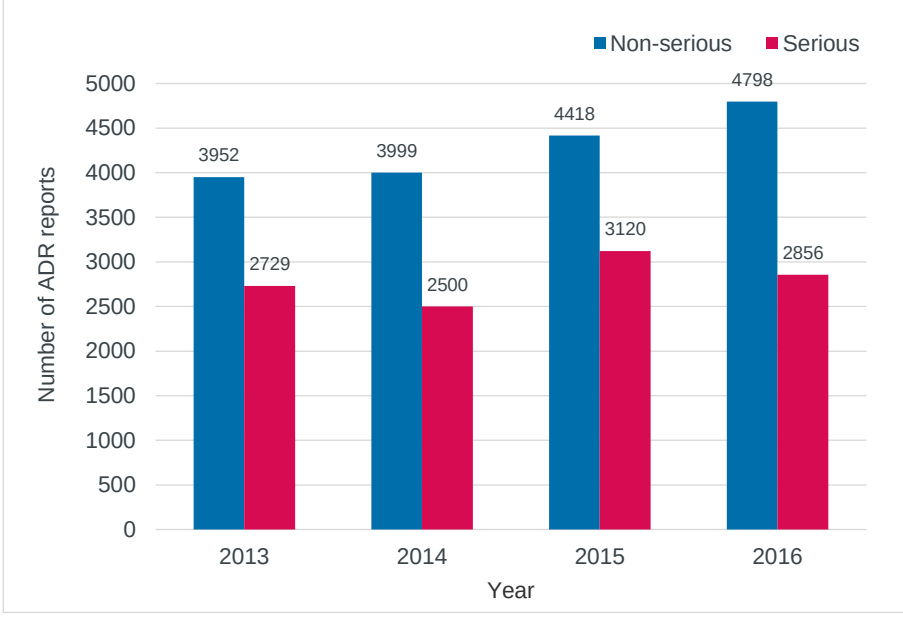

FIGURE 1. DEVELOPMENT IN THE NUMBER OF ADR REPORTS SUBMITTED TO THE DKMA FROM 2013-2016 BY SEVERITY.

[3] The 7654 ADR reports include reports submitted to the DKMA more than once, so-called duplicates. Duplicates may occur when, for example, both the physician and the patient report the adverse reaction.

[4] An ADR report is serious when one or more of the adverse reactions are serious. A serious adverse reaction is a reaction that results in death, is life-threatening, requires hospitalisation or prolongation of hospitalisation, or which results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Still many ADR reports from medicine users and their representatives
The share of ADR reports from medicine users, their representatives and the Patient Compensation Association combined keeps growing. In recent years, this group has reported more than one third of the total number of ADR reports. In 2016, they accounted for 38% of the ADR reports, of which 26% were reported by patients and their representatives, and 12% by the Patient Compensation Association.

Especially the share of ADR reports from lawyers increased in 2016, which can be ascribed to our collaboration with the Patient Compensation Association. The Patient Compensation Association forwards reported cases of pharmaceutical injuries to the DKMA when reports concern adverse reactions. The Patient Compensation Association has in recent years – and especially in 2016 – received many reports about granulomas in children after vaccination. This is reflected in the reporting statistics.

Decline in reports from physicians
Like previous years, the majority of ADR reports were from physicians in 2016. This year, they accounted for 41% of the total number of ADR reports, which is slightly lower than the previous years.

After a small increase in 2015 (11% of the total number of ADR reports), the share of reports from general practitioners fell in 2016 to the level of 2014 when they accounted for 8% of the total number of submitted ADR reports.

ADR reports from other healthcare professionals (pharmacists, midwives and nurses) accounted for 21% of ADR reports in 2016, which is at the same level as the previous years.

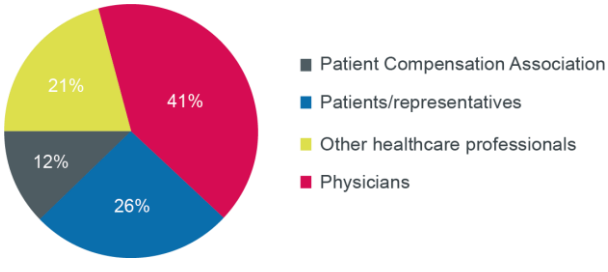

FIGURE 2. SHARE OF ADR REPORTS BY REPORTER TYPE IN 2016

Fewer reports from the regions
Of the total 7654 ADR reports we received in 2016, 1454 came from hospitals in Denmark. This is a 17% decrease compared to 2015.

The highest percentage fall was recorded in Region Zealand (32%), followed by the Region of Southern Denmark (23%), the Capital Region of Denmark (17%) and the Central Denmark Region (10%). The North Denmark Region (16%) recorded a small increase in ADR reports, but it should be noted that this region, like previous years, submits very few ADR reports compared to the other regions.

The reports from hospitals in the Capital Region of Denmark still account for more than half of all ADR reports from the regions.

Recent years have shown a clear trend that regions with an ADR manager role report far more adverse reactions than the regions with no ADR manager role. ADR managers, who help physicians with the reporting of adverse reactions, have been employed with the Capital Region of Denmark since 2013 and with Region Zealand since 2014.

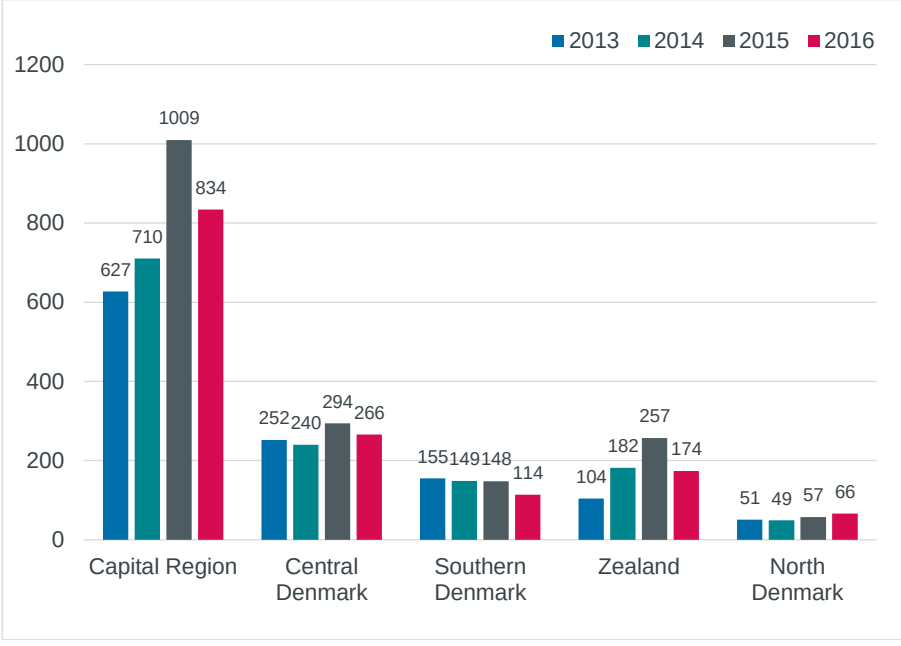

FIGURE 3. ADR REPORTS FROM THE DANISH REGIONS IN 2013-2016.[5]

Easier and better reporting with an ADR manager

An ADR manager makes it considerably easier and faster for hospital physicians to report suspected adverse reactions. Physicians need only to state the patient's name and civil registration number, the suspected drug, dose and adverse reaction as well as the hospital and department names, and the ADR manager then submits the ADR report to the DKMA.

Since the ADR managers have great knowledge of the DKMA's reporting system, their ADR reports are generally more detailed and complete, which reduces the need for follow-up questions compared to the other ADR reports and improves quality. The DKMA will therefore continue its close collaboration with the ADR managers in coming years, but will also aim to extend the ADR manager role to the remaining regions to get more and better ADR reports.

Web service makes it easy to report suspected adverse reactions

In 2014, the DKMA launched a web service that makes it easier for physicians to report suspected adverse reactions to the DKMA. We hope that more physicians will use the web service, thereby contributing to a better safety overview of medicines marketed in Denmark.

With the web service, physicians can report suspected adverse reactions directly from one of the systems they use every day, like an electronic patient record at the hospital or medical practice, without having to enter a number of basic information about themselves, the patient and the medicine the patient is taking.

Read more about the web service: *NSP Service: Adverse reaction reporting*

[5] We received an additional two ADR reports from hospitals in Greenland that are not included in the figure.

4 Good quality ADR reports

ADR reports provide the foundation for, among other things, signal generation and many investigations into pharmaceutical safety issues. It is therefore important that the ADR reports have a high quality, and that data are as complete as possible. For this reason, we focus on achieving high quality ADR reports and work continuously to improve quality assurance processes. With assistance from a pharmacist student, we have been working on a project aimed to measure the quality of the ADR reports by means of the so-called *vigiGrade Completeness Score* – a score developed by the WHO. The project showed, among other things, that the ADR reports submitted directly to the DKMA from e.g. health professionals and citizens, typically via an e-form, had a significantly higher quality than those submitted via the pharmaceutical companies. If key information is missing in an ADR report, the DKMA may need to request supplementary information later on. It requires a lot of resources, and the DKMA is therefore working out ways to improve the quality as far as possible at the time of reporting to reduce the need for obtaining supplementary information.

The results from the project were presented at the WHO's 39th Annual Meeting of National Pharmacovigilance Centres. See the DKMA's poster here: *Major differences in report quality in directly and indirectly reported ICSRs and no effect of follow-up information on report quality was found by using the vigiGrade Completeness Score algorithm*

5 ADR signals 2016

Every week, the DKMA monitors ADR reports to detect possible new ADR signals and other problems specific to pharmaceutical safety and inappropriate use.

An ADR signal reflects a new possible causal relationship between an adverse reaction and a certain type of medicine or a new angle on an already known causality. Signals may originate from ADR reports and a variety of other sources, e.g. monitoring programmes, scientific literature, specific studies, drug regulatory authorities in other countries, the media or from citizens and healthcare professionals.

Signals about new (not already known) types of adverse reactions are forwarded in the EU system to the Pharmacovigilance Risk Assessment Committee, PRAC, or the EU member state with overall responsibility for authorisation and monitoring of the medicine. Table 1 describes the Danish ADR signals that the DKMA closed and forwarded in the EU system in 2016.

Medicine	Signal	Source	Status and informative action
Zyrtec (cetirizine)	Intense itching and/or urticaria after discontinuation	ADR reports	The signal was closed earlier, but was reopened, and in the summer of 2016, a warning was inserted in the summary of product characteristics for Zyrtec with effect in 26 European countries. Article in Danish Pharmacovigilance Update.
Paracetamol	Possible effects on hormones and reduction in female fertility	Danish researchers published animal trials that were commented in the daily press.	Following an assessment and investigation at EU level, the signal was rejected due to weak animal testing.

TABLE 2. DANISH ADR SIGNALS FORWARDED IN THE EU SYSTEM IN 2016.

The DKMA is also concerned with ensuring appropriate use of medicine in clinical practice, and we use ADR reports, and other information, to identify inappropriate use of medicine that could be harmful to patients. For example, we check if a certain type of medicine is prescribed to the right patients, and whether any of its established precautions for use are not complied with exposing patients to discomfort and adverse reactions. ADR reports are often suited to identify problems of this nature, and together with the valuable Danish health registers, we are in a good position to evaluate them and assess the extent of the problem. Table 2 describes the other problems related to adverse reactions and inappropriate pharmaceutical use that the DKMA focused highly on in 2016.

Medicine	Safety issue	Source	Status and informative action
Antipsychotics	Antipsychotic medicines associated with diabetic ketoacidosis	ADR reports	Article in scientific journal and article in Danish Pharmacovigilance Update 2016.
Aripiprazole	Neurological, metabolic and psychiatric adverse reactions in children and adolescents treated with aripiprazole	ADR reports	Article in scientific journal and article in Danish Pharmacovigilance Update 2016.
Pregabalin	Pregabalin and abuse potential	ADR reports	Article in scientific journal and article in Danish Pharmacovigilance Update 2016.
ADHD drugs	Cardiovascular adverse reactions	ADR reports	Article in Danish Pharmacovigilance Update 2016
SSRIs	SSRIs and oral cavities	Approaches from medicine users	Article in Danish Pharmacovigilance Update 2016
Childhood vaccines	Confusion between vaccines in the childhood immunisation programme	ADR reports and events from the Danish patient safety database	Article in Danish Pharmacovigilance Update coordinated with the Danish Patient Safety Authority.
Kenalog	Double vision in patients who as part of off-label treatment had a suspension with plaque formation injected	ADR reports	The parallel importer has been ordered to tighten its control with the product to avoid plaque formation.

TABLE 3. PROBLEMS RELATED TO ADVERSE REACTIONS AND INAPPROPRIATE PHARMACEUTICAL USE IN 2016.

6 Focus on the monitoring of certain types of medicines

Along with our weekly monitoring of ADR reports, the DKMA is extra alert to medicines that require special attention for whatever reason. This is the case with reports of suspected adverse reactions related to vaccines in the Danish childhood immunisation programme, contraceptive pills, melatonin for children and adolescents and biological medicines and biosimilars.

Childhood vaccines
All ADR reports involving vaccines in the Danish childhood immunisation programme are every quarter assessed by a paediatrician and reviewed by a vaccination panel of relevant

experts. The assessments are published on the DKMA website and in the newsletter Danish Pharmacovigilance Update.

In 2016, we received a total of 1073 ADR reports about childhood vaccines, of which 237 were serious (figure 1).

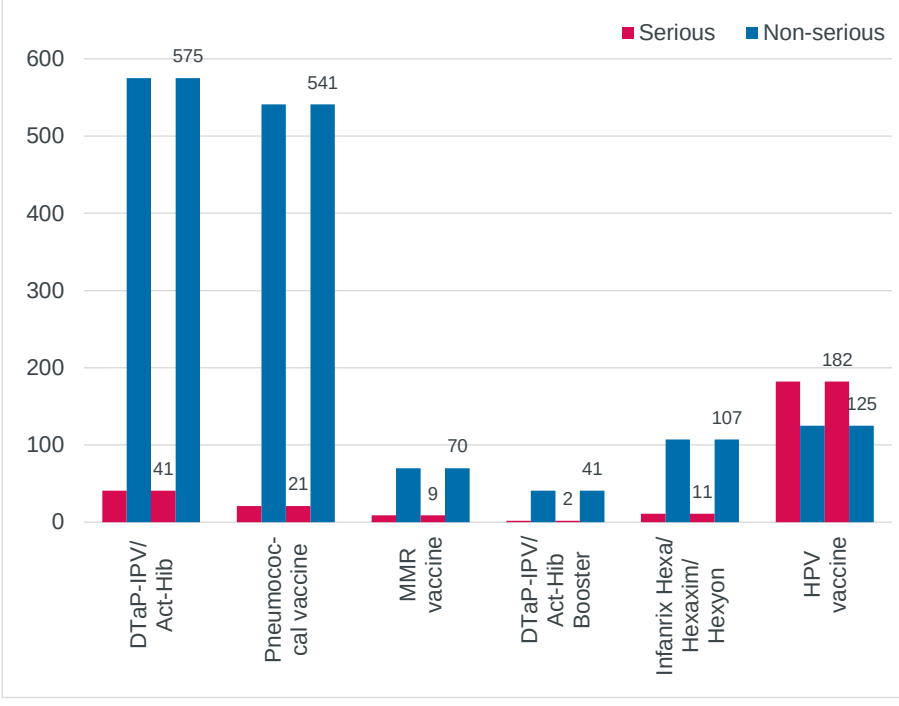

FIGURE 4: ADR REPORTS ABOUT VACCINES IN THE CHILDHOOD IMMUNISATION PROGRAMME.[6]

Many ADR reports about granulomas

There were particularly many ADR reports about granulomas after vaccination with aluminium-containing vaccines: 632 ADR reports about granulomas, and 384 ADR reports about aluminium allergy, which was an increase of 123% compared to 2015. Granulomas were predominantly reported as adverse reactions to the DTap-IPV/Act-Hib vaccine and the pneumococcal vaccine. The majority of the ADR reports about granulomas involved granulomas that had occurred before 2016, but reported in 2016 primarily via the Patient Compensation Association.

Drop in ADR reports about HPV vaccines

We received a total of 307 reports about suspected adverse reactions related to the HPV vaccines. This was significantly less than the 822 ADR reports submitted in 2015.

182 of the ADR reports were serious. Whereas ten of the ADR reports involved suspected adverse reactions to the 2-valent HPV vaccine Cervarix, the other involved the 4-valent HPV vaccines Gardasil and Silgard.

[6] One ADR report about DT-IPV/Act-Hib, given to a child in 1990, is included in the DTap-IPV/Act-Hib reports.

The most frequently reported symptoms were fatigue, headache, dizziness and nausea. Quite many of the ADR reports also described joint and muscle symptoms such as pain and muscle weakness. Palpitations and concentration problems were also among the most frequently reported symptoms.

Like the ADR reports about granulomas, the vast majority of ADR reports involving HPV vaccines concerned adverse reactions that had occurred several years back. 17 ADR reports described girls vaccinated in 2016, while the remaining 290 ADR reports described girls vaccinated in 2012 and 2013.

Contraceptive pills
The DKMA always keeps close watch on contraceptive pills because it is a medicine that is given to healthy persons with a preventive aim.

In 2016, we investigated why several women continue on 3rd and 4th generation contraceptive pills instead of switching to 1st and 2nd generation contraceptive pills. We looked into how users of contraceptive pills switch between the different generations. Our investigation prompted us to follow up on our previous report on contraceptive pills and the risk of blood clots. We based our investigation on the following:

- The scientific literature on contraceptive pills and thromboembolic complications
- Contraceptive pill consumption among women who had redeemed a prescription for contraceptive pills in the period 2011-2014 and suspected adverse reactions related to contraceptive pills reported in the same period.

The analyses combined did not alter the DKMA's previous recommendation to prescribe 2nd generation contraceptive pills as first choice in general.

The DKMA’s report (in Danish only): *Analysis of contraceptive pills focusing on users and ADR reports of blood clots in Denmark*.

Melatonin
We put renewed focus on the use of melatonin in children and adolescents in response to new consumption data that revealed a rise in the use of melatonin among children and adolescents aged between 0 and 17 years.

In the autumn of 2016, we published three analyses which formed the basis for an assessment of the safety profile of melatonin use in children and adolescents (all reports are in Danish only):

- *Melatonin – users between 0-17 years of melatonin-containing medicines*
- *Possible unintended effect on sexual maturation – a literature study*
- *Adverse reactions in children and adolescents – a literature study*.

The analyses combined did not give rise to further measures.

Biological medicines and biosimilars
The introduction of biosimilar medicinal products on the market in 2015 created a need to ensure good quality information and assurance for patients. A separate action plan for this area was therefore formulated with the DKMA at the helm. During the course of 2016, the action plan was effected through specific activities within several areas to achieve a targeted and product-specific monitoring of new biosimilar medicines with the ultimate aim of ensuring safe and secure treatment for patients:

- Specific activities to encourage monitoring at product level

- An information campaign to increase understanding among health professionals about product-specific monitoring and to raise the citizens' confidence in the use of the products
- Promotion of digital solutions at hospitals and in medical practices to make ADR reporting easier for health professionals
- Special focus by the DKMA on monitoring the safe use of these medicines.

The DKMA has published a report (in Danish only) with its experiences and results of the combined efforts: *ADR reports on and the use of selected biological medicinal products*.

Great international interest in the DKMA's work with biosimilar medicines
In the spring of 2016, we participated in three international conferences on the topic of biosimilar medicinal products. There was a keen interest to hear about the DKMA's action plan in relation to safety monitoring of biosimilar medicines. Especially our information efforts in the area aroused curiosity, and we were praised from several sides for our work with user involvement and efforts to find out what kind of information patients and relatives need. On request, we wrote an article on our work with the action plan based on our presentations. The article was published in the scientific Journal, GaBI journals; Generics and Biosimilars Initiative Journal.

The article is available here: *Pharmacovigilance on biologicals and biosimilars: a Danish perspective*

7 Evaluating the effectiveness of Danish risk minimisation measures

The DKMA has for many years worked on a Danish model for effectiveness measurement of risk minimisation efforts adapted to the Danish health service and the potentials of the unique Danish health data. Risk minimisation efforts could take many forms. For example, it could be different types of safety information or restrictions in the prescription or dispensing of a medicine that aim to reduce adverse reactions and discomforts for patients who take the medicine.

Based on data from the DKMA's previous monitoring project for dabigatran etexilate, we investigated if the model and statistical method could be used to evaluate the effect of a safety announcement issued by the EMA about dose adjustment of dabigatran etexilate in elderly patients to avoid severe bleeding in patients. The work was conducted in collaboration with the Thrombosis Research Unit at Aalborg University Hospital. The results were presented internationally at the 32nd International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE). The DKMA has furthermore written a scientific publication, which was brought in the internationally recognised scientific journal, Pharmacoepidemiology and Drug Safety, titled: "*Evaluating the effectiveness of risk minimisation measures: the application of a conceptual framework to Danish real-world dabigatran data*".

We will now do further work to develop a model and statistical methods for systematic effectiveness measurement of risk minimisation measures that can be tested on additional measures in future with the purpose of future implementation in the DKMA's routine activities.

8 New access to better overviews of reported suspected adverse reactions

In 2016, the DKMA introduced Interactive Adverse Drug Reaction (ADR) overviews which are a new web-based tool that offers researches and anyone interested better possibilities of searching for reported suspected adverse reactions. The ADR overviews were developed in collaboration with the British medicines agency, MHRA, which makes the same tool available to its stakeholders.

For several years, the DKMA has facilitated access to data on reported adverse reactions in PDF format, but now we have launched an interactive version that makes it possible to filter by age, year, gender, severity, etc. It is also possible to filter by reporter, e.g. by healthcare professional or by patients and their representatives.

The new web-based tool is accessible from the DKMA website via the page *Interactive Adverse Drug Reaction overviews.*

9 Joint European efforts in pharmacovigilance

A significant share of the DKMA's work with pharmacovigilance takes place jointly with the other European drug regulatory authorities to ensure we obtain the best possible data basis for monitoring and to learn from other countries' work with risk communication, signal detection and so forth.

The DKMA is an active player in this international pharmacovigilance collaboration, and we spearhead the safety reviews of a line of medicinal products under the European Pharmacovigilance Risk Assessment Committee, PRAC.

PRAC continually monitors safety aspects of marketed medicines and plans how to best avoid or minimise risks of new medicines.

The DKMA publishes the results of the most important PRAC conclusions in the monthly newsletter Danish Pharmacovigilance Update as well as ad hoc announcements. Often, this results in changes to the summary of product characteristics and package leaflet and as relevant, the issue of a Direct Healthcare Professional Communication (DHPC) and the initiation of further investigations.

DKMA acts as adviser in the European Scientific Advice Working Party
One of the DKMA's representatives in PRAC has since October 2015 been a member of the European Scientific Advice Working Party (SAWP), which offers scientific advice to companies in connection with the preparation of trial protocols, among other things for the so-called PASS studies (Post-authorisation Safety Studies). PASS studies are studies carried out on already marketed medicines to analyse a possible safety risk or to verify the safety profile

of a given medicine. In 2016, safety related advice in SAWP was required in only a few cases, but it is expected that the demand for advice will increase once the companies become aware of the possibility.

Major European project on top-class pharmacovigilance
For three years, the DKMA has been an active partner and has helped achieve results in the European SCOPE Joint Action project in the pharmacovigilance area. Through close collaboration between the European medicine regulators, the purpose of the SCOPE project was to share expertise and examples of good practice as well as develop tools and guidelines for the benefit of pharmacovigilance and patient safety at the national and European levels. The work finished in 2016 after three years intensive project work, and the results have been presented regularly in international contexts.

SCOPE has exploited the benefits of broad collaboration across the EU to improve pharmacovigilance. Routed in the ambitious drug monitoring legislation from 2010, the aim has been to help all national medicine regulators to develop skills and capacity in pharmacovigilance for the benefit of the entire EU network and patient safety. The project has been a platform for interaction and has strengthened the collaboration between EU drug regulatory authorities.

The project was concluded with a line of workshops aimed to increase awareness of the possibilities to report suspected adverse reactions to the authorities.

The material and further information about SCOPE Joint Action are available at *www.scopejointaction.eu*.

10 Strategy for further work with pharmacovigilance

In 2016, the DKMA formulated a new strategy for the entire Agency and five strategies within each of the following five sub-areas: medicines licensing, medicines control, pharmacovigilance, medicines supply and medical devices.

Strengthened pharmacovigilance
Henceforth, we will increasingly take a risk-based and efficient approach to pharmacovigilance to make optimum use of the available resources for the benefit of medicine users. To achieve this, we must make sure we are the preferred partner within pharmaceutical safety in Denmark to ensure we become involved when new potential safety issues emerge.

We must pay considerable efforts to involve medicine users when we assess pharmaceutical safety and inform the outcome to healthcare professionals and medicine users.

Our aim is to play a leading role in signal detection and analysis in Europe through new methods for ADR reporting that will ease the reporting of adverse reactions and enhance usability, and by redeveloping our pharmacovigilance database, optimising the use of register-based data and preparing a strategy for the use of big data in pharmacovigilance. We will strengthen patient safety through new methods to collect and share risk information and minimise risk, ensure systematic effectiveness measurement, and improve the safety when two or more medicines are used together (interactions).